3-22-00 A

PTO/SB/05 (2/98)
Approved for use through 09/30/2000. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Please type a plus sign (+) inside this box → +

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37C F.R §1 53(b))

Attorney Docket No.	PC10244A
First Named Inventor or Application Identifier	R. S. OBACH
Title	USE OF CYP2D6 INHIBITORS IN COMBINATION THERAPIES
Express Mail Label No.	EL 163 958 140 US

APPLICATION ELEMENTS
See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: **Assistant Commissioner for Patents, Box Patent Application, Washington, DC 20231**

1. ☒ *Fee Transmittal Form (e.g., PTO/SB/17)* ***(Submit an original, and a duplicate for fee processing)***
2. ☒ Specification [Total Pages 17]
   (preferred arrangement set forth below)
   - Descriptive title of the Invention
   - Cross References to Related Applications
   - Statement Regarding Fed sponsored R&D
   - Reference in Microfiche Appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings *(if filed)*
   - Detailed Description
   - Claim(s)
   - Abstract of the Disclosure
3. ☐ Drawing(s) *(35 U.S.C. 11.3)*[Total sheets]
4. ☒ Oath or Declaration [Total pages 2]
   a. ☒ Newly executed (original or copy)
   b. ☐ Copy from a prior application (37 CFR §1.63(d))
   (for continuation/divisional with Box 17 completed)
   [Note Box 5 below]
   i. ☐ DELETION OF INVENTOR(S)
   Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. §§1.63(d)(2) and 1.33(b).
5. ☐ Incorporation By Reference *(useable if Box 4b is checked)*
   The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered to be part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
6. ☐ Microfiche Computer Program *(Appendix)*
7. Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all necessary)*
   a. ☐ Computer Readable Copy
   b. ☐ Paper Copy (identical to computer copy)
   c. ☐ Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

8. ☐ Assignment Papers (cover sheet & document(s))
9. ☐ 37 C.F.R. §3.73(b) Statement ☒ Power of Attorney *(when there is an assignee)*
10. ☐ English Translation Document *(if applicable)*
11. ☐ Information Disclosure Statement (IDS)/PTO-1449 ☐ Copies of IDS Citations
12. ☐ Preliminary Amendment
13. ☒ Return Receipt Postcard (MPEP 503) *(Should be specifically itemized)*
14. ☐ *Small Entity Statement(s) *(PTO/SB/09-12)* ☐ Statement filed in prior application, Status still proper and desired
15. ☐ Certified Copy of Priority Document(s) *(if foreign priority is claimed)*
14. ☒ Other: Priority Claim
    U.S. Ser. No. 60/128,136, filed 04/07/1999

NOTE FOR ITEMS 1 & 14: IN ORDER TO BE ENTITLED TO PAY SMALL ENTITY FEES, A SMALL ENTITY STATEMENT IS REQUIRED (37 C.F.R. § 1.27), EXCEPT IF ONE FILED IN A PRIOR APPLICATION IS RELIED UPON (37 C.F.R. § 1.28).

17. **If a CONTINUING APPLICATION,** *check appropriate box, and supply the requisite information below and in a preliminary amendment:*
☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No: ____/____

Prior application information: *Examiner* _____ *Group/Art Unit:* _____

18. CORRESPONDENCE ADDRESS

☐ *Customer Number or Bar Code Label* ***(Insert Customer No. or Attach bar code label here)*** ***or*** ☒ *Correspondence address below*

Name	Paul H. Ginsburg				
Address	Pfizer Inc				
Address	235 East 42nd Street, 20th Floor				
City	New York	State	New York	Zip Code	10017-5755
Country	United States Of America	Telephone	(212)573-2369	Fax	(212)573-1939

NAME (Print/type)	ROY F. WALDRON	*Registration No. (Attorney/Agent)*	42,208
Signature		*Date*	MARCH 21, 2000

EXPRESS MAIL LABEL NO. EL 163 958 140 US

EXPRESS MAIL CERTIFICATION

"EXPRESS MAIL" Label No. EL 163 958 140 US, Date of Deposit: MARCH 21, 2000. I hereby certify that the accompanying UTILITY PATENT APPLICATION TRANSMITTAL, PATENT APPLICATION (17 pp.), FEE TRANSMITTAL SHEET, DECLARATION AND POWER OF ATTORNEY for PFIZER DOCKET NO. PC10244A is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to: Assistant Commissioner for Patents, BOX PATENT APPLICATION, Washington, D.C. 20231.

By _____

(Signature of person transmitting and mailing)

ROY F. WALDRON

(Typed or printed name of person)

USE OF CYP2D6 INHIBITORS IN COMBINATION THERAPIES

Background

This invention relates to the use of a CYP2D6 inhibitor in combination with a drug having CYP2D6 catalyzed metabolism in order to improve the drug's pharmacokinetic profile.

The clearance of drugs in humans can occur by several mechanisms, such as metabolism, excretion in urine, excretion in bile, etc. Despite the many types of clearance mechanisms, a large proportion of drugs are eliminated in humans via hepatic metabolism. Hepatic metabolism can consist of oxidative (e.g., hydroxylation, heteroatom dealkylation) and conjugative (e.g., glucuronidation, acetylation) reactions. Again, despite the many possibilities of types of metabolic reactions, a preponderance of drugs are metabolized via oxidative pathways. Thus, the primary route of clearance of a vast majority of drugs is oxidative hepatic metabolism.

Of the enzymes involved in the oxidative metabolism of drugs, the cytochrome P-450 (CYP) superfamily of enzymes are major contributors. CYP constitutes a class of over 200 enzymes that are able to catalyze a variety of types of oxidative reactions (via a hypothesized common reaction mechanism) on a wide range of xenobiotic substrate structures. In humans, the CYP catalyzed metabolism of most drugs is carried out by one of five isoforms: CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4, with the latter three being the most important of these enzymes.

Of all of the known human CYP isoforms, the most highly developed knowledge base of substrate specificity is for CYP2D6. This isoform is almost exclusively involved in the oxidative metabolism of lipophilic amine drugs. Well known CYP2D6 substrates include neuroleptics, type 1C antiarrhythmics, ß-blockers, antidepressants (tricyclic antidepressants, selective serotonin reuptake inhibitors and monoamine oxidase inhibitors), and others such as codeine and dextromethorphan. This apparent specificity for amines as substrates is hypothesized to arise from the presence of an acidic amino acid residue in the substrate binding site. This residue can form an ionic interaction with amine substrates while positioning sites for oxidation in propinquity to the reactive iron center of the heme of CYP. Structure activity relationships for CYP2D6 and the metabolism of amines have led to the development of a predictive model for this enzyme which states that the position of oxidation of a CYP2D6 substrate is 5 to 7 Å from the basic amine nitrogen. Some additional steric requirements are also hypothesized.

Many compounds for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation commonly exhibit one or more detrimental characteristics with regard to human pharmacokinetics. These characteristics are: (1) wide disparity in exposure between individuals possessing and lacking a copy of the CYP2D6 gene

("extensive and poor metabolizers"); (2) high inter-individual variability in exposure among extensive metabolizers; (3) propensity for supraproportional dose-exposure relationships; (4) frequent drug-drug interactions; and (5) short half-lives and poor oral bioavailability due to extensive first-pass hepatic clearance.

While not all CYP2D6 substrates possess these characteristics, most CYP2D6 substrates are subject to one or more.

In the mid-1980s observations were made concerning the disparity in exposure to drugs in a small subset of the population. In some cases, the high exposures observed in the minority of individuals were also associated with adverse reactions. These observations led to the discovery of the CYP2D6 genetic polymorphism. The CYP2D6 gene is absent in 5-10% of the Caucasian population (referred to as poor metabolizers or PM's). Such individuals can be distinguished from the rest of the population (extensive metabolizers or EM's) by an examination of genotype through restriction fragment length polymorphism analysis or through determination of phenotype by measurement of the urinary dextrorphan/ dextromethorphan ratio after administration of the latter compound. When population histograms of exposure to prototypical CYP2D6-cleared compounds are constructed, a bimodal distribution is observed. For example, the mean terminal phase half-life of propafenone, a well known CYP2D6 cleared compound, is 5.5 hours in extensive metabolizers, but is 17.2 hours in poor metabolizers. EM-PM differences are typically exacerbated upon oral administration of CYP2D6 cleared compounds due to wide disparities in first-pass extraction. Propafenone exposure after oral administration is 4.2-fold greater in PM's vs. EM's. Thus, CYP2D6 cleared compounds can be subject to increased incidences of adverse effects, due to elevated systemic exposures observed in PM's.

Regardless of the genetic polymorphism, a high degree of interindividual variability exists in the exposure to CYP2D6 cleared compounds among those individuals considered to be extensive metabolizers. While a reason for this variability is not presently known, it does not appear to be due to an increase in CYP2D6 gene copy number (although one such genotype has been reported in the literature in Sweden), nor does it appear to be due to environmental factors as this CYP isoform has never been demonstrated to be inducible. An example of this variability phenomenon is demonstrated by the exposure to the antidepressant agent imipramine and its metabolite desipramine, which demonstrates a 20-fold range of steady state plasma concentrations after oral administration. For compounds with wide therapeutic indices, this variability may not be problematic. However, if the therapeutic index for a CYP2D6 cleared compound approaches 10, increased incidences of adverse effects are likely to be observed.

Metabolic clearance is a potentially saturable process. The *intrinsic* clearance (Cl'_{int}, the ability of an organ to clear a compound without constraints imposed by organ blood flow or plasma protein binding) is a function of Michaelis-Menten parameters:

$$\frac{1}{\text{oral exposure}} \propto Cl'_{int} = \frac{V_{max}}{K_M + [S]}$$

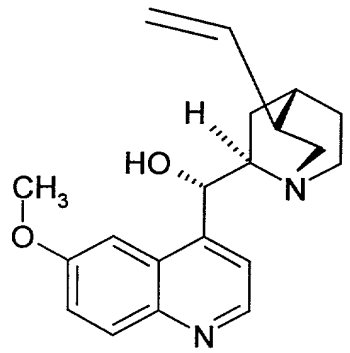
where both V_{max} and K_M are fixed constants and [S] represents the concentration of the drug in the clearing organ. For most drugs, concentrations of drug typically attained *in vivo* are well below the K_M and thus the denominator of the above expression degenerates to a constant value of K_M. However, for many CYP2D6 catalyzed reactions, K_M values are typically low. This is hypothesized to be due to the strong (relative to other CYP enzymes) ionic bond formation between cationic amine substrates and an anionic amino acid in the substrate binding site of CYP2D6. Thus for compounds cleared by CYP2D6, drug concentrations can approach and exceed K_M values resulting in intrinsic clearance values that decrease with increasing drug concentration. Since drug concentration is related to dose, clearance is observed to decrease with increasing dose. With decreases in clearance with increases in dose, exposure is thus observed to increase in a supraproportional manner with increasing dose. Such a relationship has been described in the scientific literature for the CYP2D6 cleared compounds propafenone and paroxetine. Interestingly, this phenomenon is not observed in poor metabolizers, since the CYP2D6 isoform is not present in these individuals.

The parameter K_M is a complex function of enzymatic rate constants that, for CYP, has a strong component of substrate binding rate constants. The potential exists that competitive inhibition of the metabolism of one drug can occur via catalytically competent substrate binding of a second drug. Since the K_M for CYP enzymes are closely related to binding constants, they approximate K_i values in many cases. For CYP2D6, low K_M values for typical substrates can also result in low K_i values for these same substrates as competitive inhibitors. Low K_i values reflect a greater potential to result in drug-drug interactions, since lower concentrations and doses of drug are adequate to exhibit inhibition. Thus, the potential for drug-drug interactions is a more likely concern with CYP2D6 substrates than other CYP substrates, due to the greater binding affinities of the former. Thus, since K_i values typically track K_M values, the potential for drug-drug interactions usually go hand-in-hand with the potential for supraproportional dose-exposure relationships.

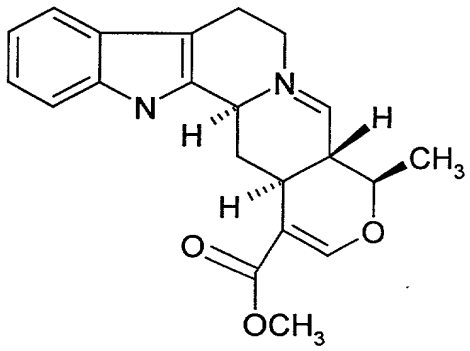
As mentioned above, clearance is related to the term V_{max}/K_M. For compounds with similar V_{max} values, the lower the value for K_M, the higher the clearance. Since many CYP2D6 substrates have very low K_M values, these compounds, as a class, are more likely to exhibit high hepatic clearance *in vivo*. High hepatic clearance results in shorter half-lives. It

also results in greater first-pass hepatic extraction which can result in low oral bioavailabilities. This point is represented by the compounds (7S,9S)-2-(2-pyrimidyl)-7-(succinamidomethyl)-prehydro-1H-pyrido-[1,2-a]pyrazine) ("sunipetron") (K_M of about 1 μM, human half-life of about 1 hour), (2S,3S)-2-phenyl-3-(2-methoxyphenyl)-methylaminopiperidine (K_M of about 1 μM, human half-life of about 4.7 hours), (1S,2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol (K_M of about 3-4 μM, human half-life of about 3-4 hours), and (2S,3S)-2-phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)-methylamino-piperidine (K_M of about 1 μM, human half-life of about 8 hours), all of which are CYP2D6 substrates. The former two compounds have K_M values in the 1 μM range. The human half-lives for these two compounds are 1.1 and 4.7 hours, and human oral bioavailability values for these two compounds are 4.6 and 1.0%, respectively. The clearance values for the former two compounds, measured after intravenous administration to humans, are in the range of blood-flow limiting values, suggesting that hepatic extraction exceeds 90%.

There are several compounds known to inhibit CYP2D6 reactions, either by 'pure' inhibition or by acting as competitive substrates. Unlike many other CYP enzymes, there are some potent inhibitors known for CYP2D6. Again, it is believed that the ionic interaction between the cationic amine group of the inhibitor and the anionic amino acid residue of CYP2D6 is at least partially responsible for the potency of CYP2D6 inhibitors. Two examples of potent CYP2D6 inhibitors are quinidine and ajmalacine:



quinidine, K_i = 80 nM



ajmalacine, K_i = 4.6 nM

Quinidine represents a commonly utilized antiarrhythmic agent whereas ajmalacine is a less well-known natural product with vasodilation activity. Since quinidine is a commonly administered substance, drug interaction studies have been conducted *in vivo* for this drug and CYP2D6 cleared compounds. Quinidine has the effect of converting an extensive metabolizer to the poor metabolizer phenotype via inhibition of CYP2D6.

In addition, extracts of St. John's wort have recently been found to contain constituent substances that exhibit CYP inhibitory activity, including inhibition of CYP2D6. Examples of

constituent substances of St. John's extract that exhibit CYP inhibitory activity are hyperforin, I3, II8-biapigenin, hypericin, and quercetin. Other unidentified components also exhibit CYP inhibitory activity.

For CYP2D6 cleared compounds, the problem that is frequently focused on is the disparity in the exposures between extensive and poor metabolizers and the high variability demonstrated by the extensive metabolizers. However, what is commonly overlooked is the fact that these compounds typically have very satisfactory pharmacokinetics in the poor metabolizers. In subjects lacking the CYP2D6 enzyme, CYP2D6 cleared compounds: (1) typically have long $t_{1/2}$ values and high oral bioavailability and (2) do not exhibit supraproportional dose-exposure relationships. By lacking the CYP2D6 enzyme, the variability of drug exposures in poor metabolizers is no greater than variabilities exhibited by non-CYP2D6 cleared compounds. Although attempts have been made to link poor metabolizer status with proclivity to various pathological states, a definitive cause-effect relationship has yet to be established. Thus, since poor metabolizers represent a normal and healthy segment of the population, it is not anticipated that converting extensive metabolizers to poor metabolizers via administration of a specific CYP2D6 inhibitor would result in any untoward effects related to inhibition of this enzyme.

This invention relates to the coformulation or combined use of a CYP2D6 inhibitor and a CYP2D6 cleared compound. Thus, instead of avoiding a drug-drug interaction, this invention involves developing such an interaction intentionally in order to improve the pharmacokinetics of therapeutically useful, but pharmacokinetically flawed compounds. Such an approach is analogous to the utilization of sustained-release formulations to enhance the pharmacokinetics of drugs. However, instead of modulating drug elimination via input rate limitation, this approach seeks to do the same by modulating the elimination rate directly. Furthermore, in addition to lengthening half-life, a CYP2D6 inhibitor would enhance oral exposure due to a suppression of hepatic first-pass extraction.

Summary of the Invention

This invention relates to a method of administering a drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation (also referred to throughout this document as a "Therapeutic Drug"), or a pharmaceutically acceptable salt thereof, in combination with a CYP2D6 inhibitor, or a pharmaceutically acceptable salt thereof, to a human in need of the intended pharmaceutical activity of such drug, wherein the Therapeutic Drug and the CYP2D6 inhibitor are not the same compound. The above method is hereinafter referred to as the "Combination Method".

This invention also relates to the Combination Method, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation is a

selective serotonin reuptake inhibitor containing a primary, secondary or tertiary alkylamine moiety (e.g., sertraline or fluoxetine).

This invention also relates to the Combination Method, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation is an NMDA (N-methyl-D-aspartate) receptor antagonist containing a primary, secondary or tertiary alkylamine moiety.

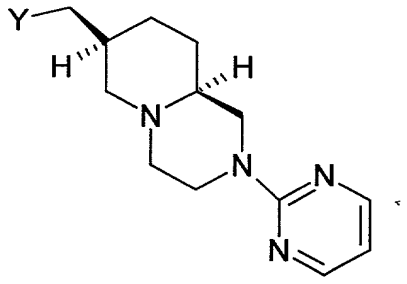
This invention also relates to the Combination Method, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation is a neurokinin-1 (NK-1) receptor antagonist containing a primary, secondary or tertiary alkylamine moiety.

This invention also relates to the Combination Method, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation is a tricyclic antidepressant containing a primary, secondary or tertiary alkylamine moiety (e.g., desipramine, imipramine or clomipramine).

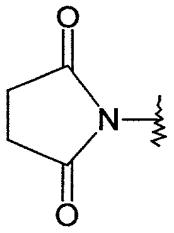
A preferred embodiment of this invention relates to the Combination Method, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation, is (2S,3S)-2-phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylamino-piperidine or a pharmaceutically acceptable salt thereof.

A preferred embodiment of this invention relates to the Combination Method, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation, is sunipetron or a pharmaceutically acceptable salt thereof.

Sunipetron has the following structure



wherein Y is a group of the formula



Another preferred embodiment of this invention relates to the Combination Method, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation is (1S, 2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol or a pharmaceutically acceptable salt thereof.

Examples of other drugs for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation are the following: mequitazine (J. Pharmacol. Exp. Ther., 284, 437-442 (1998)); tamsulosin (Xenobiotica, 28, 909-22 (1998)); oxybutynin (Pharmacogen., 8, 449-51 (1998)); ritonavir (Clin. PK, 35, 275-291 (1998)); iloperidone (J. Pharmacol. Exp. Ther., 286, 1285-93 (1998)); ibogaine (Drug Metab. Dispos., 26, 764-8 (1998)); delavirdine (Drug Metab. Dispos., 26, 631-9 (1998)); tolteridine (Clin. Pharmcol. Ther., 63, 529-39 (1998)); promethazine (Rinshoyakon, 29, 231-38 (1998)); pimozide, J. Pharmacol. Exp. Ther., 285, 428-37 (1998)); epinastine (Res. Comm. Md. Path. Pharmacol., 98, 273-92 (1997)); tramodol (Eur. J. Clin. Pharm., 53, 235-239 (1997)); procainamide (Pharmacogenetics, 7, 381-90 (1997)); methamphetamine (Drug Metab. Dispos., 25,1059-64 (1997)); tamoxifen (Cancer Res., 57, 3402-06 (1997)); nicergoline (Br. J. Pharm., 42, 707-11 (1996)); and fluoxetine (Clin. Pharmcol. Ther., 60, 512-21 (1996)). All of the foregoing references are incorporated herein by references in their entireties.

Examples of other drugs for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation, all of which are referred to, along with their respective pathways of CPY2D6 mediated oxidative biotransformation (e.g., O-demethylation, hydroxylation, etc.), by M. F. Fromm et al. in Advanced Drug Delivery Reviews, 27, 171-199 (1997), are the following: alprenolol, amiflamine, amitriptyline, aprindine, brofaromine, buturalol, cinnarizine, clomipramine, codeine, debrisoquine, desipramine, desmethylcitalopram, dexfenfluramine, dextromethorphan, dihydrocodine, dolasetron, encainide, ethylmorphine, flecainide, flunarizine, fluvoxamine, guanoxan, haloperidol, hydrocodone, indoramin, imipramine, maprotiline, methoxyamphetamine, methoxyphenamine, methylenedioxymethamphetamine, metoprolol, mexiletine, mianserin, minaprine, procodeine, nortriptyline, N-propylajmaline, ondansetron, oxycodone, paroxetine, perhexiline, perphenazine, phenformine, promethazine, propafenone, propanolol, risperidone, sparteine, thioridazine, timolol, tomoxetine, tropisetron, venlafaxine and zuclopenthixol.

Other preferred embodiments of this invention relate to the Combination Method wherein the CYP2D6 inhibitor, or pharmaceutically acceptable salt thereof, that is employed in such method is quinidine or ajmalacine or a pharmaceutically acceptable salt of one of these compounds.

Other embodiments of this invention relate to the Combination Method, wherein the CYP2D6 inhibitor, or pharmaceutically acceptable salt thereof, that is employed in such method, is selected from the following compounds and their pharmaceutically acceptable

salts: sertraline (J. Clin. Psychopharm., 18, 55-61 (1998)); venlafaxine (Br. J. Pharm., 43, 619-26 (1997)); dexmedetomidine (DMD, 25, 651-55 (1997)); tripennelamine, premethazine, hydroxyzine, (Drug Metab. Dispos., 26, 531-39 (1998)); halofrintane and chloroquine, (Br. J. Clin. Pharm., 45, 315-(1998)); and moclobemide (Psychopharm., 135, 22-26 (1998)).

A further embodiment of this invention relates to the Combination Method wherein the CYP2D6 inhibitor that is employed in such method is St. John's wort or an extract or constituent thereof.

This invention also relates to a pharmaceutical composition comprising:

(a) a therapeutically effective amount of a drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation (also referred to throughout this document as a "Therapeutic Drug"), or a pharmaceutically acceptable salt thereof;

(b) an amount of a CYP2D6 inhibitor, or a pharmaceutically acceptable salt thereof, that is effective in treating the disorder or condition for which the Therapeutic Drug referred to in (a) is intended to treat; and

(c) a pharmaceutically acceptable carrier;

wherein said drug and said CYP2D6 inhibitor are not the same compound.

The above pharmaceutical composition is hereinafter referred to as the "Combination Pharmaceutical Composition".

Preferred embodiments of this invention relate to Combination Pharmaceutical Compositions wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation, or pharmaceutically acceptable salt thereof, that is contained in such pharmaceutical composition is (2S, 3S)-2-phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylaminopiperidine or a pharmaceutically acceptable salt thereof.

Other preferred embodiments of this invention relate to Combination Pharmaceutical Compositions wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation, or pharmaceutically acceptable salt thereof, that is contained in such pharmaceutical composition is (1S, 2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol or a pharmaceutically acceptable salt thereof.

Other preferred embodiments of this invention relate to Combination Pharmaceutical Compositions wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation, or pharmaceutically acceptable salt thereof, that is contained in such pharmaceutical composition is sunipetron or a pharmaceutically acceptable salt thereof.

Other embodiments of this invention relate to Combination Pharmaceutical Compositions wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation, or pharmaceutically acceptable salt thereof,

that is contained in such compositions is selected from the following compounds and their pharmaceutically acceptable salts: mequitazine (J. Pharmacol. Exp. Ther., 284, 437-442 (1998)); tamsulosin (Xenobiotica, 28, 909-22 (1998)); oxybutynin (Pharmacogen., 8, 449-51 (1998)); ritonavir (Clin. PK, 35, 275-291 (1998)); iloperidone (J. Pharmacol. Exp. Ther., 286, 1285-93 (1998)); ibogaine (Drug Metab. Dispos., 26, 764-8 (1998)); delavirdine (Drug Metab. Dispos., 26, 631-9 (1998)); tolteridine (Clin. Pharmcol. Ther., 63, 529-39 (1998)); promethazine (Rinshoyakon, 29, 231-38 (1998)); pimozide, J. Pharmacol. Exp. Ther., 285, 428-37 (1998)); epinastine (Res. Comm. Md. Path. Pharmacol., 98, 273-92 (1997)); tramodol (Eur. J. Clin. Pharm., 53, 235-239 (1997)); procainamide (Pharmacogenetics, 7, 381-90 (1997)); methamphetamine (Drug Metab. Dispos., 25,1059-64 (1997)); tamoxifen (Cancer Res., 57, 3402-06 (1997)); nicergoline (Br. J. Pharm., 42, 707-11 (1996)); and fluoxetine (Clin. Pharmcol. Ther., 60, 512-21 (1996)). All of the foregoing references are incorporated herein by references in their entireties.

Other embodiments of this invention relate to Combination Pharmaceutical Compositions wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation, or pharmaceutically acceptable salt thereof, that is contained in such compositions is selected from the following compounds and their pharmaceutically acceptable salts, all of which are referred to, along with their respective pathways of CYP2D6 mediated oxidative biotransformation (e.g., O-demethylation, hydroxylation, etc.), by M. F. Fromm et al. in Advanced Drug Delivery Reviews, 27, 171-199 (1997): alprenolol, amiflamine, amitriptyline, aprindine, brofaromine, buturalol, cinnarizine, clomipramine, codeine, debrisoquine, desipramine, desmethylcitalopram, dexfenfluramine, dextromethorphan, dihydrocodine, dolasetron, encainide, ethylmorphine, flecainide, flunarizine, fluvoxamine, guanoxan, haloperidol, hydrocodone, indoramin, imipramine, maprotiline, methoxyamphetamine, methoxyphenamine, methylenedioxymethamphetamine, metoprolol, mexiletine, mianserin, minaprine, procodeine, nortriptyline, N-propylajmaline, ondansetron, oxycodone, paroxetine, perhexiline, perphenazine, phenformine, promethazine, propafenone, propanolol, risperidone, sparteine, thioridazine, timolol, tomoxetine, tropisetron, venlafaxine and zuclopenthixol.

Other embodiments of this invention relate to Combination Pharmaceutical Compositions wherein the CYP2D6 inhibitor, or pharmaceutically acceptable salt thereof, that is contained in such composition is selected from the following compounds and their pharmaceutically acceptable salts: sertraline (J. Clin. Psychopharm., 18, 55-61 (1998)); venlafaxine (Br. J. Pharm., 43, 619-26 (1997)); dexmedetomidine (DMD, 25, 651-55 (1997)); tripennelamine, premethazine, hydroxyzine, (Drug Metab. Dispos., 26, 531-39 (1998)); halofrintane and chloroquine, (Br. J. Clin. Pharm., 45, 315-(1998)); and moclobemide (Psychopharm., 135, 22-26 (1998)).

A further embodiment of this invention relates to the Combination Method wherein the CYP2D6 inhibitor that is employed in such method is St. John's wort or an extract or constituent thereof.

This invention also relates to a Combination Pharmaceutical Composition, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation is a selective serotonin reuptake inhibitor containing a primary, secondary or tertiary alkylamine moiety (e.g., sertraline or fluoxetine).

This invention also relates to a Combination Pharmaceutical Composition, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation is an NMDA (N-methyl-D-aspartate) receptor antagonist containing a primary, secondary or tertiary alkylamine moiety.

This invention also relates to a Combination Pharmaceutical Composition, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation is an a neurokinin-1(NK-1) receptor antagonist containing a primary, secondary or tertiary alkylamine moiety.

This invention also relates to a Combination Pharmaceutical Composition, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation is a tricyclic antidepressant containing a primary, secondary or tertiary alkylamine moiety (e.g., desipramine, imipramine or clomipramine).

The term "treatment", as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such condition or disorder. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

The term "CYP2D6 mediated oxidative transformation", as used herein, refers to the CYP2D6 catalyzed oxidation reactions (e.g., benzylic, aromatic or aliphatic hydroxylation, O-dealkylation, N-dealkylation, sidechain, sulfoxidation) through which metabolism of CPY2D6 substrate drugs proceeds.

Detailed Description of the Invention

This invention relates both to Combination Methods, as defined above, in which the Therapeutic Drug, or pharmaceutically acceptable salt thereof, and the CYP2D6 inhibitor, or pharmaceutically acceptable salt thereof, are administered together, as part of the same pharmaceutical composition, and to Combination Methods in which these two active agents are administered separately as part of an appropriate dose regimen designed to obtain the benefits of the combination therapy.

The appropriate dose regimen, the amount of each dose administered, and specific intervals between doses of each active agent will depend on the patient being treated, and the source and severity of the condition. Generally, in carrying out the methods of this invention, the

Therapeutic Drug will be administered in an amount ranging from one order of magnitude less than the amount that is known to be efficacious and therapeutically acceptable for use of the Therapeutic Drug alone (i.e., as a single active agent) to the amount that is known to be efficacious and therapeutically acceptable for use of the Therapeutic Drug alone. For example, (2S,3S)-2-phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylaminopiperidine will generally be administered to an average weight (approximately 70 kg) adult human in an amount ranging from about 5 to about 1500 mg per day, in single or divided doses, preferably from about 0.07 to about 21 mg/kg. (1S, 2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol or a pharmaceutically acceptable salt thereof will generally be administered to an average weight adult human in an amount ranging from about 0.02 to about 250 mg per day, in single or divided doses, preferably from about 0.15 to about 250 mg per day. Sunipetron will generally be administered to an average weight adult human in an amount ranging from about 2 to about 200 mg per day, in single or divided doses. Variations may nevertheless occur depending upon the physical condition of the patient being treated and his or her individual response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration throughout the day.

The Therapeutic Drugs, e.g., (7S,9S)-2-(2-pyrimidyl)-7-(succinamidomethyl)-prehydro-1H-pyrido-[1,2-a]pyrazine) ("sunipetron"), (2S,3S)-2-phenyl-3-(2-methoxyphenyl)-methylaminopiperidine, (1S,2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol, (2S,3S)-2-phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylaminopiperidine, and the CYP2D6 inhibitor compounds and their pharmaceutically acceptable salts (both the Therapeutic Drugs and the CYP2D6 inhibitors, as well as their pharmaceutically acceptable salts, hereinafter, also referred to individually or collectively, as "active agents") can each be administered separately or can be administered together, each or both in combination with pharmaceutically acceptable carriers or diluents in single or multiple doses. More particularly, such agents can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, each or both of the foregoing active agents is present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration, solutions of either or both of the active agents, or pharmaceutically acceptable salts thereof, employed in the methods of this invention in either sesame or peanut oil or in aqueous propylene glycol may be used. The aqueous solutions should be suitably buffered (preferably pH greater than 8) if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

Additionally, it is also possible to administer either or both the active agents, or pharmaceutically acceptable salts thereof, employed in the methods of this invention topically when treating inflammatory conditions of the skin, and this may be done by way of creams, jellies, gels, pastes, patches, ointments and the like, in accordance with standard pharmaceutical practice.

Whether a person is a "poor metabolizer" or an "extensive metabolizer" can be determined by measuring the concentrations of the drug dextromethorphan and its metabolite dextrorphan in the person's blood, urine or saliva after passage of a period of time following administration of the drug. A dextromethorphan/dextrorphan ratio of less than 0.3 defines an extensive metabolizer, while the same ratio greater than or equal to 0.3 defines a poor metabolizer. Suitable periods of time to wait after administration of the drug for this type of phenotyping are: from about 4 to 8 hours for urine measurements, 2 to 8 hours for plasma measurements and three to 8 hours for saliva measurements. Such a method is described by Schmidt et al., Clin. Pharmacol. Ther., 38, 618, 1985.

The following protocol can be used to determine the impact that coadministration of a CYP2D6 inhibitor with a Therapeutic Drug, as defined above, would have on the pharmacokinetics of the Therapeutic Drug.

Method:

1. Subjects that are predetermined to be extensive metabolizers (EMs; those individuals with functional CYP2D6 activity) are administered an oral dose of a compound being tested as a CYP2D6 inhibitor.

2. Concomitantly, or at some predetermined time period after the dose of the CYP2D6 inhibitor, these subjects are administered a dose of a drug known to be primarily cleared via CYP2D6 mediated metabolism.

3. At times of 0 hour (predose) and at predetermined time points after administration of the CYP2D6 cleared compound, several blood samples are taken from each subject. An example of sampling times would be 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, and 72 hours.

4. The blood (or plasma or serum) is analyzed for the CYP2D6 cleared compound using a specific bioanalytical method (such as HPLC with UV or MS detection).

5. The blood concentrations of the CYP2D6 cleared compound are plotted vs time, and pharmacokinetics are calculated from these data. The pharmacokinetic parameters to be measured are the area under the concentration vs. time curve (AUC), maximum concentration (C_{max}), time of maximum concentration (T_{max}), clearance (CL), and half-life ($t_{1/2}$).

6. A second leg of the experiment involves dosing the same subjects with the CYP2D6 cleared compound in the absence of the CYP2D6 inhibitor. Steps 3-5 are repeated. (The order of the two legs of this study is not important, as long as a suitable washout period is applied.)

7. The concentration vs. time plots and the pharmacokinetic parameters from the two legs of the study are compared and the effect of the CYP2D6 inhibitor assessed by this comparison.

CLAIMS

1. A method of administering a drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation, or a pharmaceutically acceptable salt thereof, in combination with a CYP2D6 inhibitor, or a pharmaceutically acceptable salt thereof, to a human in need of the intended pharmaceutical activity of such drug, wherein said drug and said CYP2D6 inhibitor are not the same compound.

2. A method according to claim 1 wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation is a selective serotonin reuptake inhibitor containing a primary, secondary or tertiary alkylamine moiety or a pharmaceutically acceptable salt thereof.

3. A method according to claim 1 wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation is an NMDA receptor antagonist containing a primary, secondary or tertiary alkylamine moiety or a pharmaceutically acceptable salt thereof.

4. A method according to claim 1 wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation is a neurokinin-1 (NK-1) receptor antagonist containing a primary, secondary or tertiary alkylamine moiety or a pharmaceutically acceptable salt thereof.

5. A method according to claim 1 wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation is a tricyclic antidepressant containing a primary, secondary or tertiary alkylamine moiety or a pharmaceutically acceptable salt thereof.

6. A method according to claim 1, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation is (2S,3S)-2-phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylamino-piperidine, or a pharmaceutically acceptable salt thereof.

7. A method according to claim 1, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation is (1S, 2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol or a pharmaceutically acceptable salt thereof.

8. A method according to claim 1, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation is sunipetron or a pharmaceutically acceptable salt thereof.

9. A method according to claim 1, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation is selected from the group consisting of mequitazine, tamsulosin, oxybutynin, ritonavir, iloperidone, ibogaine, delavirdine, tolteridine, promethazine, pimozide, epinastine, tramodol, procainamide,

methamphetamine, tamoxifen, nicergoline, fluoxetine, and pharmaceutically acceptable salts thereof.

10. A method according to claim 1, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation is selected from the group consisting of alprenolol, amiflamine, amitriptyline, aprindine, brofaromine, buturalol, cinnarizine, clomipramine, codeine, debrisoquine, desipramine, desmethylcitalopram, dexfenfluramine, dextromethorphan, dihydrocodine, dolasetron, encainide, ethylmorphine, flecainide, flunarizine, fluvoxamine, guanoxan, haloperidol, hydrocodone, indoramin, imipramine, maprotiline, methoxyamphetamine, methoxyphenamine, methylenedioxymethamphetamine, metoprolol, mexiletine, mianserin, minaprine, procodeine, nortriptyline, N-propylajmaline, ondansetron, oxycodone, paroxetine, perhexiline, perphenazine, phenformine, promethazine, propafenone, propanolol, risperidone, sparteine, thioridazine, timolol, tomoxetine, tropisetron, venlafaxine, zuclopenthixol, and pharmaceutically acceptable salts thereof.

11. A method according to claim 1, wherein the CYP2D6 inhibitor is quinidine, ajmalacine or pharmaceutically acceptable salts thereof.

12. A method according to claim 1, wherein the CYP2D6 inhibitor is selected from the group consisting of sertraline, venlafaxine, dexmedetomidine, tripennelamine, premethazine, hydroxyzine, halofrintane, chloroquine, moclobemide, and pharmaceutically acceptable salts thereof.

13. A method according to claim 1, wherein the CYP2D6 inhibitor is St. John's wort, or an extract or constituent thereof.

14. A pharmaceutical composition comprising:

(a) a therapeutically effective amount of a drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation, or a pharmaceutically acceptable salt thereof;

(b) an amount of a CYP2D6 inhibitor, or a pharmaceutically acceptable salt thereof, that is effective in treating the disorder or condition for which the drug referred to in "a" is intended to treat; and

(c) a pharmaceutically acceptable carrier;

wherein said drug and said CYP2D6 inhibitor are not the same compound.

15. A pharmaceutical composition according to claim 14, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation is (2S,3S)-2-phenyl-3-(2-methoxy-5-trifluoromethoxy-phenyl)methyl-aminopiperidine or a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition according to claim 14, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation is sunipetron or a pharmaceutically acceptable salt thereof.

17. A pharmaceutical composition according to claim 14, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation is (1S, 2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol or a pharmaceutically acceptable salt thereof.

18. A pharmaceutical composition according to claim 14, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation is selected from the group consisting of mequitazine, tamsulosin, oxybutynin, ritonavir, iloperidone, ibogaine, delavirdine, tolteridine, promethazine, pimozide, epinastine, tramodol, procainamide, methamphetamine, tamoxifen, nicergoline, fluoxetine, and pharmaceutically acceptable salts thereof.

19. A pharmaceutical composition according to claim 14, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation is selected from the group consisting of alprenolol, amiflamine, amitriptyline, aprindine, brofaromine, buturalol, cinnarizine, clomipramine, codeine, debrisoquine, desipramine, desmethylcitalopram, dexfenfluramine, dextromethorphan, dihydrocodine, dolasetron, encainide, ethylmorphine, flecainide, flunarizine, fluvoxamine, guanoxan, haloperidol, hydrocodone, indoramin, imipramine, maprotiline, methoxyamphetamine, methoxyphenamine, methylenedioxymethamphetamine, metoprolol, mexiletine, mianserin, minaprine, procodeine, nortriptyline, N-propylajmaline, ondansetron, oxycodone, paroxetine, perhexiline, perphenazine, phenformine, promethazine, propafenone, propanolol, risperidone, sparteine, thioridazine, timolol, tomoxetine, tropisetron, venlafaxine, zuclopenthixol and pharmaceutically acceptable salts thereof.

20. A pharmaceutical composition according to claim 14, wherein the CYP2D6 inhibitor is quinidine, ajmalacine or pharmaceutically acceptable salts thereof.

21. A pharmaceutical composition according to claim 14, wherein the CYP2D6 inhibitor is selected from the group consisting of sertraline, venlafaxine, dexmedetomidine, tripennelamine, premethazine, hydroxyzine, halofrintane, chloroquine, moclobemide, and pharmaceutically acceptable salts thereof.

22. A pharmaceutical composition according to claim 14, wherein the CYP2D6 inhibitor is St. John's wort, or an extract or constituent thereof.

USE OF CYP2D6 INHIBITORS IN COMBINATION THERAPIES

Abstract

This invention relates to the use of a CYP2D6 inhibitor in combination with a drug having CYP2D6 catalyzed metabolism, wherein the drug and the CYP2D6 inhibitor are not the same compound; and pharmaceutical compositions for said use.

PTO/SB/01(12/97)
Approved for use through 09/30/2000. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Please type a plus sign (+) inside this box → [+]

DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☒ Declaration submitted with Initial Filing

☐ Declaration Submitted after Initial Filing (surcharge 37 CFR 1.16 (e)) required)

Attorney Docket Number	PC10244A
First Named Inventor	R. SCOTT OBACH
COMPLETE IF KNOWN	
Application Number	NOT YET ASSIGNED
Filing Date	FILED HEREWITH
Group Art Unit	NOT YET ASSIGNED
Examiner Name	NOT YET ASSIGNED

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

USE OF CYP2D6 INHIBITORS IN COMBINATION THERAPIES

(Title of the Invention)

the specification of which

☒ is attached hereto

OR

☐ was filed on (MM/DD/YYYY) [ ] as United States Application Number or PCT International Application Number [ ] and was amended on (MM/DD/YYYY) [ ] (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below:

Application Number(s)	Filing Date (MM/DD/YYYY)
60/128,136	04/07/1999

☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B sheet attached hereto.

PTO/SB/01 (12/97)
Approved for use through 09/30/2000. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Please type a plus sign (+) inside this box → [+]

DECLARATION ---- Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 U.S.C. 1.56, which became available between the filing date of the prior application and the national or PCT International filing date of this application.

U.S. Parent Application Number or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number *(if applicable)*

☐ Additional U.S. or PCT International application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: ☐ Customer Number or

Place Customer Number Bar Code Label here

☒ Registered practitioner(s) name/registration number listed below

Name	Registration Number	Name	Registration Number
Peter C. Richardson	27,526	Lawrence C. Akers	28,587
Allen J. Spiegel	25,749	A. Dean Olson	31,185
Paul H. Ginsburg	28,718	Mervin E. Brokke	32,723
J. Trevor Lumb	28,567	Valerie M. Fedowich	33,688
James T. Jones	30,561	Bryan C. Zielinski	34,462
Gregg C. Benson	30,977	Robert T. Ronau	36,257
Robert F. Sheyka	31,304	B. Timothy Creagan	39,156
Grover F. Fuller Jr.	31,760	Alan L. Koller	37,371
Karen DeBenedictis	32,977	Jolene W. Appleman	35,428
Lorraine B. Ling	35,251	Kristina L. Konstas	37,864
Garth Butterfield	36,997	Seth H. Jacobs	32,140
Carl J. Goddard	39,203	Martha A. Gammill	31,820
Raymond M. Speer	26,810	Gregory P. Raymer	36,647
Jennifer A. Kispert	40,049	E. Victor Donahue	35,492
Israel Nissenbaum	27,582	Roy F. Waldron	42,208
Steven W. Collier	42,429	Todd M. Crissey	37,807
Adrian G. Looney	41,406	Deborah A. Martin	44,222

☐ Additional registered practitioner(s) named on supplemental Registered Practitioner Information sheet PTO/SB/02C attached hereto.

Direct all correspondence to: ☐ Customer Number or Bar Code Label | OR ☒ Correspondence address below

Name	Paul H. Ginsburg				
Address	Pfizer Inc				
Address	235 East 42nd Street, 20th Floor				
City	New York	**State**	New York	**Zip Code**	10017-5755
Country	United States Of America	**Telephone**	(212)573-2369	**Fax**	(212)573-1939

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname
R. SCOTT	OBACH

Inventor's Signature	R. Scott Obach					**Date**	3-13-2000
Residence: City	GALES FERRY	**State**	CT	**Country**	US	**Citizenship**	US
Post Office Address	44 EAGLE RIDGE DRIVE						
Post Office Address							
City	GALES FERRY	**State**	CT	**Zip**	06335	**Country**	US

☐ Additional inventors are being named on the _____ a supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto.